# Crossed Bisadducts in the Reaction of Pyridine with Two Different Nitrile Oxides. [1]

Franca Marinone Albini*, Rita De Franco, and Tiziano Bandiera

Dipartimento di Chimica Organica, Viale Taramelli 10,
27100 Pavia, Italy

Pierluigi Caramella*

Dipartimento di Chimica, Via Borsari 46,
44100 Ferrara, Italy

Antonino Corsaro and Giancarlo Perrini

Dipartimento di Scienze Chimiche, Viale Doria 8,
95125 Catania, Italy

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Bisadducts of some aromatic nitrile oxides to pyridine are described. Crossed adducts are formed by exposure of pyridine to a couple of different nitrile oxides.

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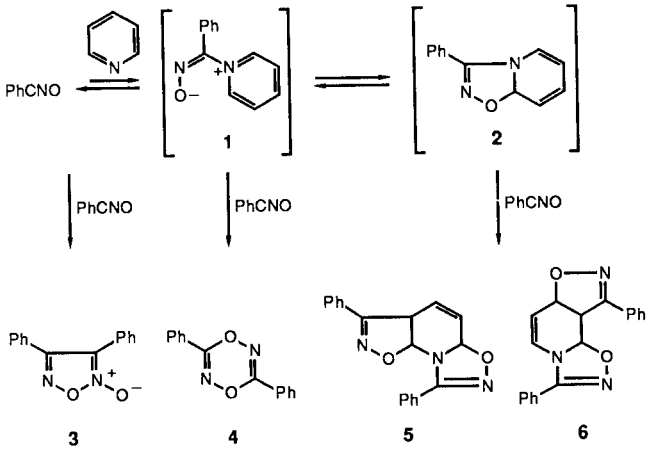
## Introduction.

In a previous paper, we reported the unexpected isolation of biscycloadducts in the reaction between pyridine and benzonitrile oxide (BNO) [2]. The nature of the products obtained in this reaction is remarkably dependent upon the polarity of the reaction solvents. While in ethanol the 1,4,2,5-dioxadiazine dimer **4** is quantitatively formed [3], in apolar solvents the two bisadducts **5** and **6** could be obtained in a 26% and 9% yield, respectively, along with furoxane **3** and some dioxadiazine **4** (Scheme 1).

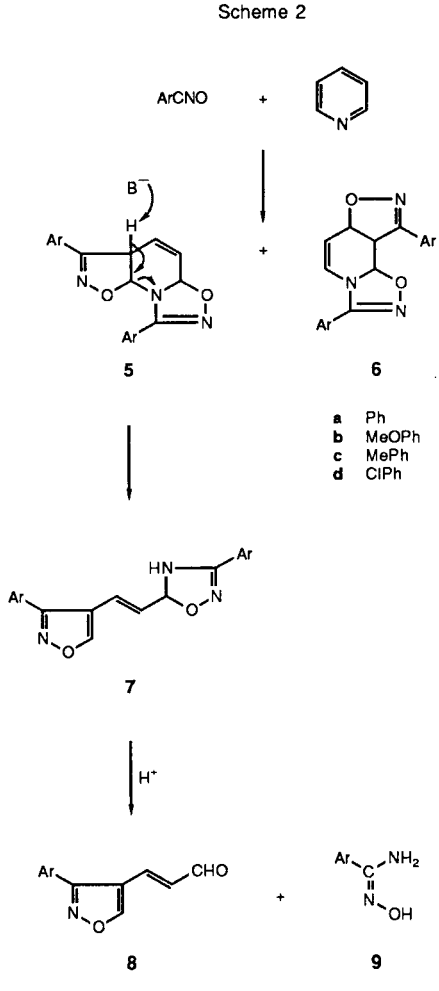
Scheme 1




The surprisingly high dipolarophilic activity of the aromatic pyridine and the large solvent effect suggested a mechanism involving two different labile intermediates, zwitterion **1** and monocycloadduct **2**. The cycloadduct is viewed as a secondary product, which derives from the zwitterion **1** in a subsequent electrocyclic closure. Although present in a very low concentration, **2** contains a rather reactive dienamine moiety and adds regiospecifically the nitrile oxide carbon at the $\beta$ and $\delta$ positions, to yield the site-isomeric biscycloadducts **5** and **6**.

In a search of more direct evidence for the proposed mechanism, we have turned for some time our attention to the trapping of the labile monocycloadduct **2** with suitable

Scheme 2



reagents, which could add to the dienaminic system of **2** [4]. The choice is obviously restricted to those reagents, which react neither with BNO nor with pyridine. *p*-Nitrophenylazide and 3,6-diphenyl-1,2,4,5-tetrazine seemed to meet the requirements. Attempts at trapping were made by performing the reaction of BNO with pyridine in benzene in the presence of 5 equivalents of *p*-nitrophenylazide and 3,6-diphenyl-1,2,4,5-tetrazine. These admittedly mild trapping agents did not, however, interfere with the formation of biscycloadducts **5** and **6**.

To solve the problem we finally decided to investigate the formation of crossed biscycloadducts, by exposing pyridine to a couple of different nitrile oxides, which yet display similar reactivities. We report here a study of the reaction of *p*-methoxy BNO (MeOBNO), *p*-methyl BNO (MeBNO) and *p*-chloro BNO (ClBNO) with pyridine. Crossed biscycloadducts could be isolated by simultaneous generation of a couple of nitrile oxides (BNO and MeOBNO) in the presence of pyridine.

## Results.

### Bisadducts.

As in the case of BNO (a), *in situ* generation of MeOBNO (b), MeBNO (c) and ClBNO (d) in the presence of 5 equivalents of pyridine afforded bisadducts **5b,c,d** and **6b,c,d**, which were isolated by column chromatography in 22-28% and 5-9% yields, respectively (Scheme 2).

The structures of the cycloadducts rely upon spectroscopic and chemical evidence. The nmr spectra of bisadducts **5b,c,d** and **6b,c,d** are almost identical with those of the analogous unsubstituted bisadducts **5a** and **6a** [2] (Table 1). The major adducts **5** show a broad double doublet at $\delta$ 4.1 for the 4-isoxazolinic proton $H_B$, while the signals of the other four non aromatic protons fall together at $\delta$ 5.9-6.5 in a complex multiplet, which could be simplified by addition of $Eu(fod)_3$ in the case of adduct **5a** [2]. The *anti* stereochemistry of the adducts follows from a recent X-ray structure of **5a** [5]. The nmr signals of the pyridine protons of the minor bisadducts **6** are well separated, and are consistent with the assigned structure. The *anti* stereochemistry of the bisadducts **6** is suggested by the large coupling constants (8.0 Hz) through the bond connecting the two five-membered heterocyclic rings.

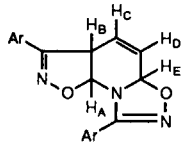
Unequivocal structure determination of the major bisadducts **5** was provided by alkaline cleavage of the tetrahydropyridine ring of the adducts, as already reported for **5a** [5]. Refluxing solutions of the adducts in ethanol in the presence of excess triethylamine afforded the products of ring opening **7b-d**, which are cleaved by acids to yield the isoxazole acryl aldehydes **8** in 60-70% yields and the amidoximes **9** (Scheme 2). The nmr data of the aldehydes **8a-d** are summarized in Table 2.

### Crossed Bisadducts.

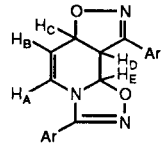
Having in our hands the "homogeneous" bisadducts **5** and **6** for the four nitrile oxides, we finally started with the trapping project. Exposure of pyridine to couples of different nitrile oxides afforded rather complex mixtures. Examination (tlc) showed in all cases the spots of the four homogeneous bisadducts along with additional spots at-

Table 1

NMR Data of Bisadducts [a]




**5**



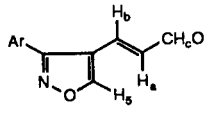

**6**

| Compound | A | B | C | D | E | $J_{AB}$ | $J_{BC}$ | $J_{CD}$ | $J_{DE}$ | other |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | 6.0-6.4 m | 4.16 dd | 6.0-6.4 m | 6.0-6.4 m | 6.0-6.4 m | 9.5 | 4.0 | - | - | |
| **5b** | 5.9-6.5 m | 4.10 dd | 5.9-6.5 m | 5.9-6.5 m | 5.9-6.5 m | 9.5 | 4.0 | - | - | $OCH_3$ 3.88 |
| **5c** | 5.9-6.5 m | 4.10 dd | 5.9-6.5 m | 5.9-6.5 m | 5.9-6.5 m | 9.5 | 4.0 | - | - | $CH_3$ 2.41 |
| **5d** | 5.9-6.5 m | 4.15 dd | 5.9-6.5 m | 5.9-6.5 m | 5.9-6.5 m | 9.5 | 4.0 | - | - | |
| **6a** | 6.80 d | 5.45 dd | 4.91 dd | 3.50 t | 5.51 d | 7.0 | 5.2 | 8.0 | 8.0 | |
| **6b** | 6.78 d | 5.33 dd | 4.87 dd | 3.42 t | 5.43 d | 7.0 | 5.0 | 8.0 | 8.0 | $OCH_3$ 3.88 |
| **6c** | 6.79 d | 5.37 dd | 4.91 dd | 3.46 t | 5.45 d | 7.6 | 5.0 | 8.0 | 8.0 | $CH_3$ 2.41, 2.43 |
| **6d** | 6.79 d | 5.45 dd | 4.95 dd | 3.48 t | 5.55 d | 7.0 | 5.0 | 8.0 | 8.0 | |
| **10** | 5.9-6.4 m | 4.10 dd | 5.9-6.4 m | 5.9-6.4 m | 5.9-6.4 m | 9.5 | 4.0 | - | - | $OCH_3$ 3.85 |
| **11** | 5.9-6.4 m | 4.10 dd | 5.9-6.4 m | 5.9-6.4 m | 5.9-6.4 m | 9.5 | 4.0 | - | - | $OCH_3$ 3.87 |
| **12** | 6.80 d | 5.41 dd | 4.92 dd | 3.52 t | 5.46 d | 8.0 | 5.0 | 8.0 | 8.0 | $OCH_3$ 3.89 |

[a] Labels of protons are given in the formulas.

Table 2

NMR Data of Aldehydes [a]



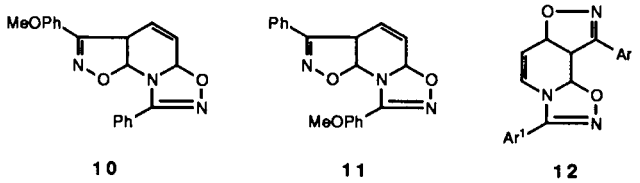
| Compound | Ar | $H_a$ | $H_b$ | $H_c$ | $H_5$ | $J_{ab}$ | $J_{ac}$ | other |
|---|---|---|---|---|---|---|---|---|
| **9a** | Ph | 6.45 | 7.25 | 9.55 | 8.78 | 16 | 7.8 | --- |
| **9b** | *p*-MeOPh | 6.50 | 7.31 | 9.63 | 8.78 | 16 | 7.8 | $CH_3O$ 3.65 |
| **9c** | *p*-MePh | 6.51 | 7.31 | 9.62 | 8.81 | 16 | 7.8 | $CH_3$ 2.45 |
| **9d** | *p*-ClPh | 6.48 | 7.25 | 9.62 | 8.81 | 16 | 7.8 | --- |

[a] Labels of the protons are given in the formula.

tributable to the crossed bisadducts.

Among the various reaction mixtures, the reaction of the BNO/MeOBNO couple with pyridine seemed to us the most promising as far as the chromatographic separation was concerned. The BNO bisadducts are well separated from the MeOBNO bisadducts, which display lower $R_f$, and in the intermediate region a neat spot was present. Column chromatography separation of this reaction mixture afforded, besides the BNO and MeOBNO adducts **5a,b** (4% each) and **6a,b** (1% each), a 1:1 mixture of the crossed bisadducts **10** and **11** (4% each), which were separated by careful fractional crystallization from diisopropyl ether, and even a representative of the crossed minor bisadducts, **12** (1%) (Scheme 3).

Scheme 3



**10** **11** **12**

Ar = Ph or MeOPh
$Ar^1$ = MeOPh or Ph

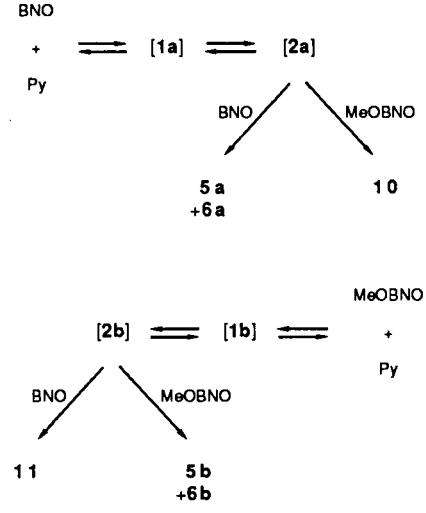
The nmr spectra of the crossed adducts are given in the last three entries of Table 1. The spectra clearly show that the adducts **10** and **11** are related to the major adducts **5**, while adduct **12** corresponds to the minor adducts **6**. The location of the aryl substituent in the major crossed adducts **10** and **11** could be established by alkaline cleavage. Adduct **10**, mp 140-142°, cleanly afforded the 3-[3(4'-methoxyphenyl)isoxazol-4-yl]-2-propenal **8b** (65%) and benzamidoxime **9a**, while adduct **11**, mp 174-175°, afforded the 3-(3-phenylisoxazol-4-yl)-2-propenal **8a** (70%) and *p*-methoxybenzamidoxime **9b**. No attempts were made to establish the exact structure of the minor crossed adduct **12**.

Final Remarks.

The closely related BNO and the three *p*-substituted BNOs behave similarly in the reactions with pyridine, affording like yields and ratios of bisadducts **5** and **6**. By exposing pyridine to the couple BNO/MeOBNO, all the possible major bisadducts, the homogeneous **5a** and **5b** and the crossed ones, **10** and **11**, were also obtained in almost identical yields.

The results of the crossing experiment clearly support the intermediacy of monocycloadducts **2**. Two labile monocycloadducts **2a** and **2b** are required to account for the product distribution. They react further with BNO or MeOBNO giving an almost statistical distribution of bisadducts (Scheme 4).

Scheme 4




Somewhat surprisingly, no selectivity was observed in the formation of the four major bisadducts. This suggests that the labile monocycloadducts **2a** and **2b** attain similar equilibrium concentrations. With respect to the unsubstituted benzonitrile oxide, the electron-donating *p*-substituent in $pOCH_3$ BNO is expected to slow down the formation of zwitterion **1b** but also facilitates its closure to monocycloadduct **2b**. As a result, the equilibrium concentration of the labile monocycloadducts depends only slightly upon the nitrile oxide *p*-substituent.

## EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. The $^1$H-nmr spectra were recorded on a Bruker WP80SY spectrometer in deuteriochloroform solutions; chemical shifts are expressed in ppm from internal tetramethylsilane ($\delta$) and coupling constants are in Hertz (Hz). The ir spectra (nujol mulls) were recorded on a Perkin-Elmer 197 spectrophotometer. Column chromatography and tlc: silicagel H 60 and $GF_{254}$ (Merck) respectively, eluant cyclo-

Table 3

Physical Data of Bisadducts

| Compound | % yield | mp° solvent | Physical aspect | Molecular Formula | Analytical data Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| **5b** | 25 | 159-161 [a] | white crystals | $C_{21}H_{13}N_3O_4$ | 66.83<br>66.58 | 5.07<br>5.00 | 11.14<br>10.99 |
| **6b** | 9 | 173-174 [b] | white crystals | $C_{21}H_{13}N_3O_4$ | 66.83<br>66.63 | 5.07<br>5.02 | 11.14<br>10.97 |
| **5c** | 22 | 149-151 [c] | white needles | $C_{21}H_{13}N_3O_2$ | 73.02<br>73.12 | 5.55<br>5.47 | 12.17<br>12.04 |
| **6c** | 5 | 125-127 [c] | yellow needles | $C_{21}H_{13}N_3O_2$ | 73.02<br>73.08 | 5.55<br>5.38 | 12.17<br>11.96 |
| **5d** | 28 | 195-197 [c] | white crystals | $C_{19}H_{13}Cl_2N_3O_2$ | 59.08<br>59.13 | 3.39<br>3.41 | 10.88<br>10.92 |
| **6d** | 8 | 154-155 [c] | white crystals | $C_{19}H_{13}Cl_2N_3O_2$ | 59.08<br>58.90 | 3.39<br>3.32 | 10.88<br>10.98 |
| **10** | 4 | 140-142 [b] | white needles | $C_{20}H_{17}N_3O_3$ | 69.15<br>69.04 | 4.93<br>4.66 | 12.10<br>11.95 |
| **11** | 4 | 174-175 [b-c] | white crystals | $C_{20}H_{17}N_3O_3$ | 69.15<br>68.90 | 4.93<br>4.91 | 12.10<br>12.00 |
| **12** | 1 | 162-164 [b] | white crystals | $C_{20}H_{17}N_3O_3$ | 69.15<br>68.86 | 4.93<br>4.68 | 12.10<br>11.87 |

[a] From ethyl acetate. [b] From diisopropyl ether. [c] From ethanol.

hexane:ethyl acetate 9:1 to 1:1.

The *p*-substituted benzhydroximic acid chlorides (*p*-methoxy, *p*-methyl, *p*-chloro) were obtained from the corresponding *p*-substituted benzaldoximes according to a literature method [6]. Treatment of the benzhydroximic acid chlorides in ethanol with excess ammonia, according to known procedures [7], afforded the *p*-substituted benzamidoximes **9b-d**. The pyridine used was freshly distilled.

General Cycloaddition Procedure.

A. Bisadducts **5b,c,d** and **6b,c,d**.

To a stirred, ice-cooled solution of the *p*-substituted benzhydroximic acid chloride (10 mmoles) and pyridine (5 equivalents) in anhydrous diethyl ether (150 ml), 1.1 equivalents of triethylamine in ether (20 ml) were added over a 0.5 hour period. After keeping 2 days at room temperature the triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure. Pyridine was azeotropically removed with excess toluene. Column chromatography separation of the residue afforded mixtures of furoxans **3** and dioxadiazines **4** [8] and then, in the order, the bisadducts **6** and **5**.

Physical characteristics and analytical data for all new compounds are reported in Table 3.

B. Crossed Bisadducts **10** and **11**.

To a stirred, ice-cooled solution of benzhydroximic acid chloride (1.55 g, 10 mmoles), *p*-methoxybenzhydroximic acid chloride (1.85 g, 10 mmoles) and pyridine (8.4 ml, 100 mmoles) in anhydrous diethyl ether (300 ml), a solution of triethylamine (3 ml, 21 mmoles) in diethyl ether (50 ml) was added dropwise in 0.5 hours. After keeping 2 days at room temperature, workup as described above afforded, in the order, the BNO bisadducts **6a**, mp 133-134° [2] (1%) and **5a**, mp 173-174° [2] (4%), the crossed minor bisadduct **12** (1%), a 1:1 mixture of the crossed major bisadducts **10** and **11** (8%) and, at last, the MeOBNO bisadducts **6b** (1%) and **5b** (4%).

The crossed bisadducts **10** and **11** are distinguishable by nmr. The more shielded protons of the disubstituted aromatic ring of **10** are a doublet at $\delta$ 6.93, while the related doublet of **11** occurs at $\delta$ 6.99. The mixture could be separated by careful fractional crystallization from diisopropyl ether. The least soluble bisadduct **10**, mp 140-142°, crystallizes first. Concentration of the mother liquors afforded the more soluble bisadduct **11**, mp 174-175°.

Alkaline Cleavage of Major Bisadducts **5b,c,d**.

To a solution of bisadducts **5b,c,d** (3 mmoles) in 25 ml of ethanol excess triethylamine (0.7 ml, 10 mmoles) was added. After refluxing 12 hours, evaporation of the solvent under reduced pressure left the crude products of ring opening **7b-d**, which were treated with ethanol containing a few drops of concentrated hydrochloric acid. After standing 3 hours at room temperature, the mixtures were diluted with water and extracted with chloroform. The extracts were dried over anhydrous sodium sulfate and evaporated to give the aldehydes **8**.

3-[3-(4'-Methoxyphenyl)isoxazol-4-yl]-2-propenal **8b**.

This compound was obtained in 68% yield, yellow crystals from diisopropyl ether, mp 114-115° (lit [9] 114-115°).

3-[3-(4'-Methylphenyl)isoxazol-4-yl]-2-propenal **8c**.

This compound was obtained in 61% yield, white crystals from diisopropyl ether, mp 109-111°.

*Anal.* Calcd. for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.97; H, 5.04; N, 6.39.

3-[3-(4'-Chlorophenyl)isoxazol-4-yl]-2-propenal **8d**.

This compound was obtained in 70% yield, yellow crystals from diisopropyl ether, mp 121-123° (lit [9] 120-122°).

The aqueous phases were neutralized with 5% sodium bicarbonate and extracted with chloroform. The extracts, after drying over anhydrous sodium sulfate and evaporation of the solvent, afforded the *p*-substituted benzamidoximes **9**.

*p*-Methoxybenzamidoxime **9b**.

This compound was obtained in 49% yield, mp 123° (lit [10] 123°).

*p*-Methylbenzamidoxime **9c**.

This compound was obtained in 43% yield, mp 147° (lit [10] 147°).

*p*-Chlorobenzamidoxime **9d**.

This compound was obtained in 49% yield, mp 134° (lit [11] 134-135°).

Compound **9b**, **9c** and **9d** were all identical with authentic specimens.

Cleavage of the Crossed Adducts **10** and **11**.

The bisadducts were cleaved with the same procedure described for **5**. Adduct **10** afforded the aldehyde **8b** (65%) and the benzamidoxime **9a**, mp 79-80° (lit [7] 79-80°) in 49% yield. The adduct **11** afforded the aldehyde **8a**, mp 73-74° (lit [9] 73-74°) in 70% yield and the *p*-methoxybenzamidoxime **9b**, mp 123° in 47% yield.

Acknowledgements.

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REFERENCES AND NOTES

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